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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/957,709	10/24/1997	HOLLY HOGREFE	1486/41363CP	2438

7590 08/24/2006

FINNEGAN, HENDERSON, FARABOW,GARRETT
& DUNNER,L.L.P
1300 I STREET N.W.
WASHINGTON, DC 20005

EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Docketed 8-28-06 Attorney MPR - MRA
Case 4121-116-9
Due Date 11-24-06 after
Action resp due 114
By IR

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	08/957,709	HOGREFE ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,46,59-66,77-79,87-89 and 95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,46,59-66,77-79,87-89 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/9/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 17, 46, 59-66, 77-79, 87-89, 95 are pending.

Applicant's amendment of claims 17, 46, 62-63, 95 in a communication filed on 6/9/2006 is acknowledged.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/9/2006 has been entered.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 6/9/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention. This is a new rejection not previously introduced.

Claim 17 is directed in part to a composition comprising a protein complex having nucleic acid polymerase enhancing activity, wherein said complex comprises a genus of *P. furiosus* proteins encoded by polynucleotides that hybridize under specific conditions to the complete complement of the nucleic acid of SEQ ID NO: 70, wherein the proteins can have any function. It is noted that the functional limitation recited in the claim refers to the entire complex. Since the complex can have any number of proteins, the functional limitation recited can be provided by any of the proteins in the complex and not necessarily by the genus of *P. furiosus* proteins encoded by polynucleotides which hybridize under the required conditions to the nucleic acid of SEQ ID NO: 70. Thus, the genus of *P. furiosus* proteins is not required to have the functional limitation associated with the complex.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, the claims encompass a functionally diverse genus of polypeptides. While the specification discloses the polynucleotide of SEQ ID NO: 70 as encoding a protein having nucleic acid polymerase enhancing activity, the specification fails to disclose (1) the structural elements in the polynucleotide of SEQ ID NO: 70 which are required in any *P. furiosus* polynucleotide encoding a polypeptide having nucleic acid polymerase enhancing activity, or (2) which proteins, in addition to a *P. furiosus* protein of any function having the structural characteristics recited are required for the complex to display nucleic acid polymerase enhancing activity

The genus of polypeptides required is potentially a genus encompassing different biological activities. While one could argue that the disclosure of the polypeptide of SEQ ID NO: 71 provides adequate description for all the members of the genus, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that mutations which result in one conservative amino acid substitution transform a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminate β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since (a) minor structural changes may result in changes affecting function, (b) there is no additional information correlating structure with nucleic acid polymerase enhancing activity, (c) there is no teaching or suggestion as to which portions of the polypeptide of SEQ ID NO: 71 are required in any *P. furiosus* protein to display polymerase enhancing activity, and (d) no information has been provided in regard to which amino acids in the polypeptide of SEQ ID NO: 71 can be modified and which ones need to be conserved to avoid loss of activity, one cannot reasonably conclude that the polypeptide of SEQ ID NO: 71 is representative of all the polypeptides recited in the claim.

Due to the fact that the specification only discloses a single species of the recited genus of proteins (i.e. SEQ ID NO: 71), and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

4. Claims 17 and 95 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein complex comprising the polypeptide encoded by the polynucleotide of SEQ ID NO: 70, does not reasonably provide enablement for a protein complex comprising (1) a *P. furiosus* polypeptide of any function which is encoded by a polynucleotide which hybridizes under the specific conditions recited to the complete complement of the polynucleotide of SEQ ID NO: 70, or (2) a polypeptide having polymerase enhancing activity encoded by a polynucleotide which hybridizes under the specific conditions recited to the complete complement of the polynucleotide of SEQ ID NO: 70. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a new rejection not previously introduced.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 17 and 95 are so broad as to encompass a protein complex having polymerase enhancing activity wherein said complex comprises (1) any *P. furiosus* polypeptide of

any function which is encoded by a polynucleotide which hybridizes under the specific conditions recited to the complete complement of the polynucleotide of SEQ ID NO: 70, or (2) a polypeptide having polymerase enhancing activity encoded by a polynucleotide which hybridizes under the specific conditions recited to the complete complement of the polynucleotide of SEQ ID NO: 70.

The genus of polynucleotides recited in claims 17 and 95 encompasses polynucleotides which can potentially encode proteins with low structural similarity. A calculation of Tm for the polynucleotides recited in claim 17 and 95 shows that under the hybridization (wash) conditions recited, the claimed polynucleotides can be approximately 87.5% sequence identical to the polynucleotide of SEQ ID NO: 70. Using the well known equation of Meinkoth and Wahl (Current Protocols in Molecular Biology, Hybridization Analysis of DNA Blots, pages 2.10.8-2.10.11, 1993), Tm = 81.5 °C +16.6x$\log_{10}$[Na+] +0.41x(%GC) - .61x(%form) – 500/L, the corresponding Tm for the polynucleotide recited is approximately 72.5 °C assuming a G+C content of 50% and L equal to 471, which is the length of SEQ ID NO: 70 (72.5 °C = 81.5 + 16.6x$\log_{10}$[3.9/200] +0.41x(%50) - 500/471; for 20xSSC the molar concentration of Na+ is 3.9). As known in the art, Tm is reduced by approximately 1 °C for each 1% mismatching, therefore under the conditions recited (0.1xSSC and 60 °C), a wash at 60 °C is equivalent to approximately 87.5% mismatching (12.5% = 72.5°C – 60°C). This level of mismatching amounts to 59 nucleotides which can be modified (59 = 0.125x471) within SEQ ID NO: 70. Thus, the genus of polynucleotides recited can potentially encompass polynucleotides encoding proteins which are 62% sequence identical to the polypeptide of SEQ ID NO: 71 since the 59 mismatches can potentially alter 59 codons (62% = 100% -59x100/156).

The enablement provided is not commensurate in scope with the claims due to the lack of knowledge as to the proteins required in the claimed complex such that it would have polymerase enhancing activity since the *P. furiosus* protein encoded by the recited polynucleotides can have any function, and the potentially large number of variants encompassed by the claims for which the

specification provides no structure that correlates with the recited function. In the instant case, the specification enables the polypeptide of SEQ ID NO: 71.

The amount of direction or guidance presented and the existence of working examples. The specification discloses the nucleotide sequence of a single polynucleotide (SEQ ID NO: 70) and the amino acid sequence of a single polypeptide (SEQ ID NO: 71) as working examples. However, the specification fails to provide any clue as to the structural elements in the polynucleotide of SEQ ID NO: 70 or the polypeptide of SEQ ID NO: 71 associated with polymerase enhancing activity or a correlation between the structures provided and the recited function.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of a polypeptide having the same biological function as that of the polypeptide of SEQ ID NO: 71. In addition, the art does not provide any teaching or guidance as to (1) which amino acids in the polypeptide of SEQ ID NO: 71 can be modified and which ones need to be conserved such that one of skill in the art can make variants as recited with the same biological activity as that of the polypeptide of SEQ ID NO: 71, (2) which segments of the polypeptide of SEQ ID NO: 71 are essential for activity, and (3) the general tolerance of proteins having polymerase enhancing activity to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by

the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for the large number of polypeptides comprising the recited structural elements encompassed by the claims. In the absence of (1) a rational and predictable scheme for modifying any amino acid in the polypeptide of SEQ ID NO: 71 such that the resulting variant would encode a protein which retains the same enzymatic activity as that of the polypeptide of SEQ ID NO: 71, and/or (2) a correlation between structure and the ability enhance polymerase activity, one of skill in the art would have to test a large number of polypeptides to determine which ones have the same function as that of the polypeptide of SEQ ID NO: 71. With regard to claim 17, one of skill in the art would have to test an infinite number of proteins to determine which ones should be included in the complex such that it would display polymerase enhancing activity since the complex as claimed does not require the *P. furiosus* protein to have that activity.

While enzymatic assays are well known in the art, and the skilled artisan can produce variants of the polypeptide of SEQ ID NO: 71 having the recited structural characteristics using well-known and widely used techniques in the art, the amount of experimentation required to enable the claimed invention is not routine due to the fact that the number of species encompassed by the claims is very large. Guo et

al.(PNAS 101(25):9205-9210, 2004) teaches that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% (*x* factor) and that this number appears to be consistent with other studies in other proteins as well (Abstract). Guo et al. further shows in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ x 100% where x is the number of mutations introduced and 0.66 is the probability of a protein to remain active after one amino acid change (0.66= 1-0.34). For example, if one were to apply this estimate to the calculated structural identity, i.e., 62% sequence identity to SEQ ID NO: 71, only $(.66)^{59}$ x 100% or 2.25 x 10^{-9}% of random mutants having 62% sequence identity to SEQ ID NO: 71 would be active. Therefore, to find a single active mutant within random mutants having 62% sequence identity to SEQ ID NO: 71, one of skill in the art would have to screen several billion mutants (100/2.25 x 10^{-9}%).

While current screening techniques in the art would allow for finding a few active mutants within several hundred thousand inactive mutants, finding a few mutants within several billion mutants, would require undue experimentation. Therefore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient

guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Double Patenting

5. Claims 17, 46, 59-66, 77-79, 87-89 and 95 remain rejected under the judicially created doctrine of double patenting over claims 1, 5-9, 13-20, 23-24, 26-34 and 40-41 of U.S. Patent No. 6,183,997. This rejection has been discussed at length in Paper No. 25, mailed on 2/27/2002.

6. Applicants have indicated that if the instant claims are found allowable, a terminal disclaimer will be filed. Since a terminal disclaimer has not yet been filed and no arguments have been presented pointing out disagreements with the Examiner's contentions, the double patenting rejection is maintained for the reasons of record.

Art of Interest

7. Dabrowski et al. (GenBank accession number AAR15897, 2003) discloses a dUTPase which comprises SEQ ID NO: 71.

Conclusion

8. No claim is in condition for allowance.

9. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
August 19, 2006

Notice of References Cited	Application/Control No. 08/957,709	Applicant(s)/Patent Under Reexamination HOGREFE ET AL.	
	Examiner Delia M. Ramirez	Art Unit 1652	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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	H	US-			
	I	US-			
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	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Meinkoth and Wahl, Current Protocols in Molecular Biology, Hybridization Analysis of DNA Blots, pages 2.10.8-2.10.11, 1993
	V	Branden et al., Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991
	W	Guo et al., PNAS 101(25):9205-9210, 2004 ✓
	X	Dabrowski et al., GenBank accession number AAR15897, 2003 ✓

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

CERTIFICATE UNDER 37 CFR § 1.10 OF MAILING BY "EXPRESS MAIL"

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June 9, 2006 — Date of Deposit

I hereby certify that this correspondence is being deposited with the United States Postal Services "Express Mail Post Office to Addressee" service under 37 CFR § 1.10 on the date indicated above and is addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: _____ Nancy Foster

IDS Form PTO/SB/08: Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	08/957,709
Filing Date	October 24, 1997
First Named Inventor	Holly HOGREFE et al.
Art Unit	1652
Examiner Name	D. Ramirez
Attorney Docket Number	04121.0116-01000

U.S. PATENTS AND PUBLISHED U.S. PATENT APPLICATIONS

Examiner Initials	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Issue or Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
DR		5,073,632	12-17-1991	Donovan	
		5,262,529	11-16-1993	Dryja et al.	
		5,449,603	09-12-1995	Nielson et al.	
		5,605,824	02-25-1997	Nielson et al.	
DR		6,183,997 B1	02-06-2001	Hogrefe	

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation[6]
DR		Attachment for 20XSSC - *cDNA Hybridization protocol using GeneTac Hybridization Unit*	
		BRANDEN et al., Introduction to Protein Structure, Garland Publishing Inc., New York, NY, page 247 (1991).	
		BROWN, *Molecular Biology Lab Fax*, BIOS Scientific Publishers, Blackwell Scientific Publications, Madison, WI, pages 140-153 (1991).	
		KENNELL, "Principles and practices of nucleic acid hybridization," *Prog. Nucl. Acid. Res. Mol. Biol.* 11:259-301 (1971).	
		HAMES et al., *Nucleic Acid Hybridization: a practical approach*, IRL Press Limited, Oxford, England, pages 76-82 (1985).	
		HUANG et al., "Fidelity and predominant mutations produced by deep vent wild-type and exonuclease-deficient DNA polymerases during *in vitro* DNA amplification," *DNA and Cell Biology*, 15:589-594 (1996).	
		UDY et al., "Microplate DNA preparation, PCR screening and cell freezing for gene targeting in embryonic stem cells," *BioTechniques*, 17(5):887-894 (1994).	
		Office Action mailed July 3, 2002, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Response filed January 3, 2003, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Office Action mailed February 14, 2003, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
DR		Amendment After Final Office Action filed June 16, 2003, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	

8/11/06

IDS Form PTO/SB/08: Substitute for form 1449A/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	08/957,709
				Filing Date	October 24, 1997
				First Named Inventor	Holly HOGREFE et al.
				Art Unit	1652
(Use as many sheets as necessary)				Examiner Name	D. Ramirez
Sheet	2	of	2	Attorney Docket Number	04121.0116-01000

NON PATENT LITERATURE DOCUMENTS			
DR		Advisory Action mailed July 30, 2003, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Amendment After Final Office Action filed March 15, 2004, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Office Action mailed April 16, 2004, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Amendment filed October 18, 2004, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Office Action mailed January 12, 2005, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Response filed July 12, 2005, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Advisory Action mailed August 23, 2005, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Response filed February 13, 2006, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Office Action mailed April 27, 2006, in U.S. Patent Application No. 09/631,613, filed August 4, 2000.	
		Office Action mailed March 25, 2003, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
		Amendment filed August 25, 2003, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
		Amendment (replacement) dated November 3, 2003, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
		Office Action mailed December 29, 2003, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
		Amendment After Final filed April 29, 2004, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
		Advisory Action mailed May 27, 2004, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
		Office Action mailed July 21, 2004, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
		Amendment filed January 21, 2005, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
		Office Action mailed April 20, 2005, in U.S. Patent Application No. 09/631,614, filed August 4, 2000.	
DR		Office Action mailed June 2, 2006, in U.S. Patent Application No. 10/738,917, filed December 16, 2003.	
BRR			

Examiner Signature		Date Considered	8/11/06

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.